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Case Report

Primary Hyperparathyroidism in a Patient With Bilateral Pheochromocytoma and a Mutation in the Tumor Suppressor *MAX*

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Abstract

Rare heterozygous loss-of-function mutations of the *MAX* gene are associated with autosomal dominant hereditary pheochromocytoma-paraganglioma syndrome. In addition, evidence suggests that pathogenic *MAX* mutation may predispose to the development of other tumors, including endocrine and nonendocrine tumors, although the number of reported cases is small. We report a 67-year-old man with bilateral pheochromocytoma, primary hyperparathyroidism, prostate cancer, neurofibroma, and abdominal wall lipoma who tested positive for a heterozygous pathogenic germline *MAX* mutation. The patient has a history of bilateral norepinephrine-producing pheochromocytomas, for which he underwent left and right adrenalectomy in his 20s and 30s, respectively. His long-standing primary hyperparathyroidism was first documented when he was 40 years old and complicated by recurrent bilateral calcium oxalate nephrolithiasis and early-onset osteoporosis. Genetic testing revealed a heterozygous pathogenic deletional frameshift mutation of the exon 4 of the *MAX* gene (c.183_195del; p.Gln62Lysfs*104). This report, together with 3 previously reported cases, suggests that germline *MAX* mutation may contribute to the development of primary hyperparathyroidism and may be considered in suspected genetic forms of this disease.

Key Words: primary hyperparathyroidism, pheochromocytoma, MAX, MYC-associated protein X

Primary hyperparathyroidism (PHPT) is a disorder of mineral metabolism that is, in its classical form, characterized by hypercalcemia and elevated or inappropriately normal parathyroid hormone (PTH) levels resulting from excessive secretion of PTH from 1 or more abnormal parathyroid glands. Over 95% of cases of PHPT are sporadic, while less than 5% have associated germline mutation that predispose to the development of parathyroid tumors [1, 2]. Familial PHPT can occur alone or as part of a syndrome. The spectrum includes multiple endocrine neoplasia (MEN) type 1 (caused by *MEN1* mutation), MEN type 2A (caused by *RET* mutation), hyperparathyroidism-jaw tumor syndrome (caused by *CDC73* mutation), and the candidate gene *GCM2* for familial isolated hyperparathyroidism [1]. Features suggestive of familial PHPT include presence of a positive family history for PHPT, young age of onset, multiglandular disease, or history of tumors that can be a component of inherited hyperparathyroidism syndromes [2, 3].

MYC-associated protein X (MAX) is an obligate heterodimerization partner for MYC family member proteins that plays an essential role in cellular proliferation [4]. Rare heterozygous loss-of-function mutations of the *MAX* gene are associated with autosomal dominant hereditary paraganglioma-pheochromocytoma syndrome [5, 6]. Evidence suggests that *MAX* mutation may predispose to the development of other tumors, for example small cell lung cancer and gastrointestinal stromal tumors. Patients have also been reported to have other endocrine tumors, such as prolactinoma, growth hormone-secreting pituitary adenoma, pancreatic neuroendocrine tumor, as well as nonendocrine tumors, such as chondrosarcoma, renal oncocytoma, and breast cancer [5-8]. Therefore, presence of multiple endocrine tumors associated with germline *MAX* mutation has been proposed to be a novel type of multiple endocrine neoplasia, although the number of reported cases is small [7]. We describe a patient with early-onset overt PHPT, an endocrine disorder that has been reported in very few individuals from families with *MAX* mutations, who was found to have bilateral pheochromocytomas and a novel germline *MAX* mutation.

Case Presentation

We report a 67-year-old man with bilateral pheochromocytoma, PHPT, prostate cancer, neurofibroma, and abdominal wall lipoma who tested positive for a heterozygous germline *MAX* mutation. He has a history of bilateral norepinephrine-producing pheochromocytomas with elevated norepinephrine level and possible aortocaval node metastasis. He first presented in his 20s with hypertension, diaphoresis, and sinus tachycardia. He was found to have a norepinephrine-producing pheochromocytoma and underwent left adrenalectomy. Several years later, he developed recurrent symptoms. Whole body MIBG scan revealed increased uptake in the right adrenal gland. He subsequently underwent right adrenalectomy in his 30s. The resulting adrenal insufficiency has been

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Table 1. Laboratory values

	Reference range and units	Recent	5 years ago	10 years ago
PTH	10-60 pg/mL (1.06-6.89 pmol/L)	161 pg/mL (H) (17.07 pmol/L)	190 pg/mL (H) (20.15 pmol/L)	135 pg/mL (H) (14.32 pmol/L)
Serum calcium	8.5-10.5 mg/dL (2.12-2.62 mmol/L)	11.4 mg/dL (H) (2.84 mmol/L)	11.6 mg/dL (H) (2.89 mmol/L)	12.2 mg/dL (H) (3.04 mmol/L)
Serum phosphorus	2.6-4.5 mg/dL (0.84-1.45 mmol/L)	2.1 mg/dL (L) (0.68 mmol/L)	1.8 mg/dL (L) (0.58 mmol/L)	2.6 mg/dL (0.84 mmol/L)
Serum magnesium	1.7-2.4 mg/dL (0.70-0.99 mmol/L)	1.5 mg/dL (L) (0.62 mmol/L)	1.7 mg/dL (L) (0.70 mmol/L)	2.6 mg/dL (1.07 mmol/L)
Serum 25(OH)D	30-100 ng/mL (75-250 nmol/L)	37 ng/mL (92 nmol/L)	21 ng/mL (L) (52 nmol/L)	23 ng/mL (L) (57 nmol/L)
Plasma calcitonin	<14.3 pg/mL (<4.18 pmol/L)	<0.5 pg/mL (<0.15 pmol/L)	<0.5 pg/mL (<0.15 pmol/L)	<0.5 pg/mL (<0.15 pmol/L)
Plasma metanephrine	<0.04 mcg/L (<0.2 nmol/L)	<0.04 mcg/L (<0.2 nmol/L)	<0.04 mcg/L (<0.2 nmol/L)	<0.04 mcg/L (<0.2 nmol/L)
Plasma normetanephrine	<0.16 mcg/L (<0.9 nmol/L)	0.26 mcg/L (H) (1.4 nmol/L)	0.51 mcg/L (H) (2.8 nmol/L)	0.53 mcg/L (H) (2.9 nmol/L)
24-h urine dopamine	65-400 mcg (424-2611 nmol)	N/A	N/A	362 mcg (2363 nmol)
24-h urine epinephrine	<21 mcg (<115 nmol)	N/A	N/A	8.8 mcg (48 nmol)
24-h urine norepinephrine	15-80 mcg (89-473 nmol)	N/A	N/A	254 mcg (1501 nmol)
24-h urine metanephrine	222-1300 mcg (1125-6591 nmol)	N/A	N/A	191 (968 nmol)
24-h urine normetanephrine	128-900 mcg (699-4912 nmol)	N/A	N/A	2343 (12 789 nmol)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; H, high; L, low; N/A, not available; PTH, parathyroid hormone.

treated with hydrocortisone 30 mg/day and fludrocortisone 0.05 mg/day. The dose of hydrocortisone was higher than the physiologic dose (10-12 mg/m^2/day) due to the patient's preference. He had negative octreotide scan and positron emission tomography-computed tomography in his early 40s. However, his urine norepinephrine and plasma normetanephrine have remained significantly elevated (Table 1). He underwent positron emission tomography-computed tomography when he was 45 years old, which revealed a 1.1 cm × 1.0 cm aortocaval lymph node with increased fluorodeoxyglucose uptake, suggestive of a metastasis of the pheochromocytoma. No surgery was performed given that he did not have symptoms and was not interested in pursuing invasive treatment.

The patient's long-standing PHPT was first documented when he was 40 years old [recent calcium of 11.4 mg/dL (2.84 mmol/L) and PTH 161 pg/mL (17.07 pmol/L), Table 1]. He has no family history of PHPT. He developed bilateral calcium oxalate nephrolithiasis first presenting with colicky pain in his 50s, and he was diagnosed with early-onset osteoporosis in his 40s with a current T-score of −4.8 in the radius. His lumbar spine and femoral neck T-scores were 0.2 and −2.1, respectively. He had been treated with alendronate for 12 years, starting when he was 44 years old, followed by drug holiday. He was restarted on alendronate when he was 65 years old and was recently switched to intravenous zoledronic acid due to gastrointestinal side effects of alendronate. On thyroid ultrasound, he has a 8 mm × 11 mm × 14 mm solid-appearing lower pole nodule of the left lobe without suspicious malignant features, which is suggestive of a possible parathyroid adenoma (Fig. 1). However, the patient was not interested in parathyroid surgery.

His medical history is also remarkable for the removal of an abdominal wall lipoma when he was 63 years old, radical prostatectomy for a prostatic adenocarcinoma with Gleason score of 7 in 2 cores and 6 in another 4 cores when he was 65, and removal of a neurofibroma of the right forearm when he was 66 years old.

Diagnostic Assessment

Given his presentation of bilateral pheochromocytomas and PHPT, a clinical diagnosis of multiple endocrine neoplasia type 2A was initially considered although with no evidence of medullary thyroid carcinoma and normal calcitonin levels (Table 1). Neurofibromatosis type 1 with incidental PHPT was also a possibility, given the presence of neurofibroma. Surprisingly, genetic panel testing, which he recently agreed to, revealed a novel heterozygous pathogenic deletional frameshift mutation in exon 4 of the *MAX* gene (c.183_195del; p.Gln62Lysfs*104; Fig. 2). This deletion leads to a shift in the open reading frame resulting in the replacement of the last 99 amino acid residues by a novel carboxyl-terminal sequence of 103 unrelated amino acids. The genetic testing was negative for other pathogenic mutations of genes associated with hereditary pheochromocytoma and paraganglioma, including *NF1*, *RET*, *SDHA*, *SDHAF1*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *VHL*.

Discussion

We report a male patient with early-onset overt PHPT and bilateral norepinephrine-producing pheochromocytomas with

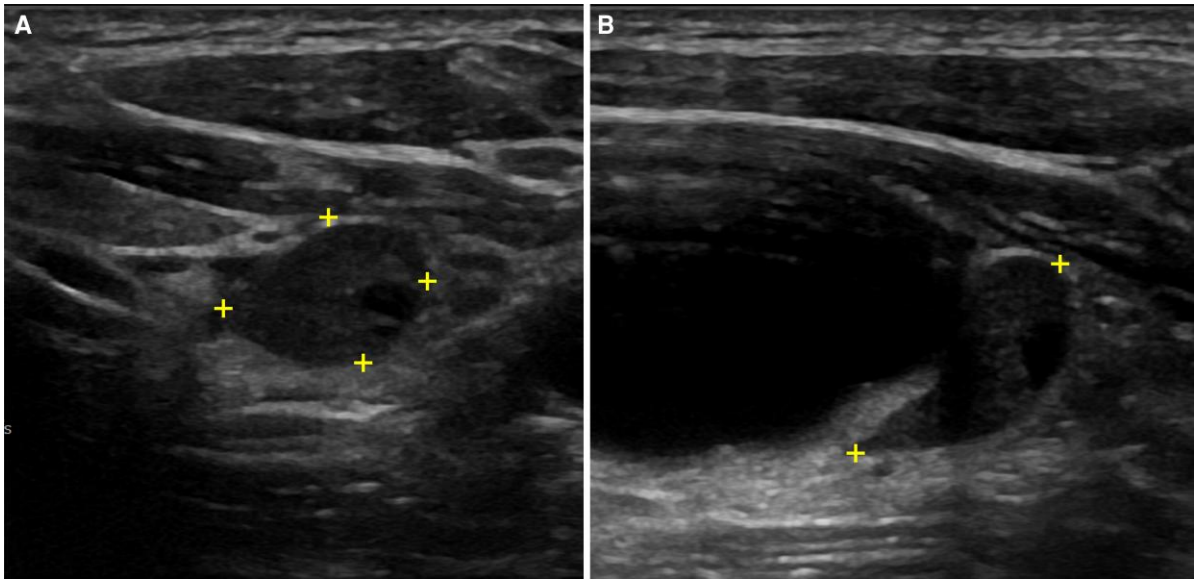

Figure 1. Thyroid ultrasound in transverse plane (A) and sagittal plane (B) showing an 8 mm × 11 mm × 14 mm solid-appearing lower pole nodule of the left lobe without suspicious malignant features suggestive of a possible parathyroid adenoma.

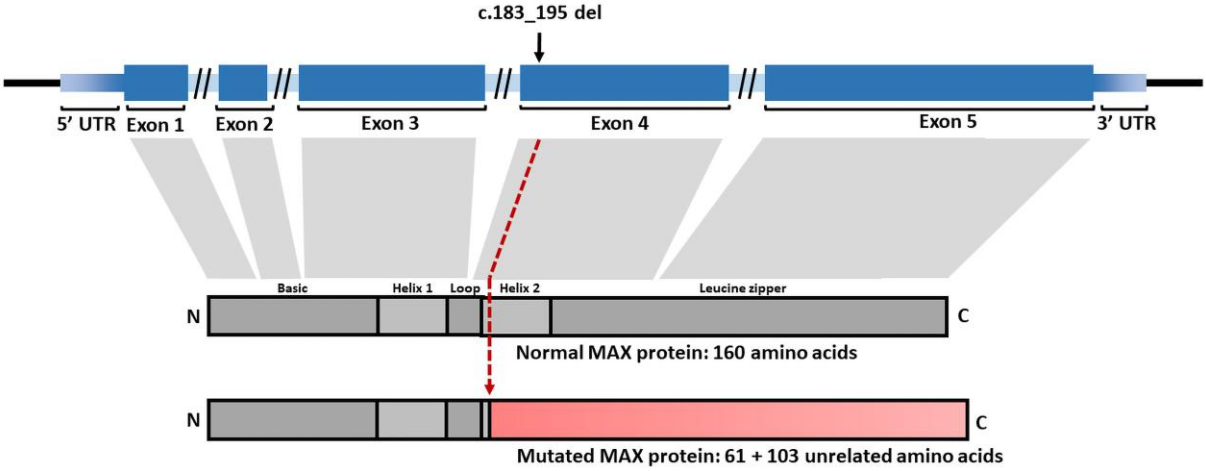

Figure 2. Schematic representation of the *MAX* mutation (c.183_195del) identified in the patient and the resulting abnormal MAX protein (p.Gln62Lysfs*104). The mutation is characterized by a deletion of the nucleotides 183 to 195, shifting the reading frame and disrupting the last 99 amino acids of the MAX protein and extending the protein by 4 additional amino acid residues.

metastasis who was found to have a novel heterozygous pathogenic deletional frameshift germline mutation in the *MAX* gene. The MAX protein is an obligate heterodimerization partner with members of the MYC family of basic helix-loop-helix leucine zipper of transcription factors [4]. It can heterodimerize with MYC to activate gene transcription and with MXD family members (MXDs, MNT) and MGA to repress transcription [9]. Depending on the context and stoichiometry between these heterodimers, loss of MAX can lead to growth arrest or tumor formation. Studies have shown that MAX functions as a tumor suppressor for certain types of tumors, including pheochromocytoma, small cell lung cancer, and gastrointestinal stromal tumor [6, 9, 10]. A recent report, which included an animal model of small cell lung cancer, identified mechanisms leading to tumor growth upon loss of MAX, which include the upregulation of genes that control serine biosynthesis and one-carbon metabolism [9].

To our knowledge, PHPT has been previously reported in only 3 patients with germline *MAX* mutations. In a case series of 28 patients with pheochromocytoma or paraganglioma who had pathogenic *MAX* mutations by Burnichon et al [5], a 18-year-old male patient with a *MAX* mutation (c.223C > T; p.Arg75*) and bilateral pheochromocytomas was reported to have PHPT. Roszko et al [8] reported a 49-year-old female patient with bilateral pheochromocytomas, prolactinoma, and a *MAX* mutation (c.296-1G > T) who had mild PHPT that resolved after resection of the pheochromocytomas. It was hypothesized that the pheochromocytomas may have produced ectopic PTH; however, immunohistochemistry of the pheochromocytoma tissue was negative for PTH. Another report by Seabrook et al [7] described a female patient with bilateral pheochromocytomas (diagnosed at 34 years), PHPT, and multiple parathyroid adenomas (diagnosed at 60 years) and a *MAX* mutation (c.22G > T; p.Glu8*). In this study, *MAX* immunohistochemistry was attempted on the parathyroid tissue samples but

was considered uninterpretable, since no staining was observed in either neoplastic cells or internal positive controls. None of the 3 reports have performed loss of heterozygosity studies in the parathyroid tissue to demonstrate the second hit of *MAX* mutation. Our report of a patient with a germline *MAX* mutation and PHPT that occurred several years after bilateral adrenalectomy adds to the literature that germline *MAX* mutation may be associated with the development of PHPT.

Our case report has a limitation as parathyroid tissue is not available for analysis. Performing immunohistochemistry to examine the presence of the MAX protein in the parathyroid tissue or loss of heterozygosity studies to the second hit in the parathyroid tissue would have helped to strengthen the case for a causal relationship. We can, therefore, not confidently implicate a *MAX* mutation as a contributing event for PHPT development. However, PHPT is most often seen in postmenopausal women; the development of this condition in a man <45 years old increases the suspicion of a genetic form of the disease [3]. Animal models investigating the impact of *MAX* mutation on the development of parathyroid tumors would be most helpful. If the causal relationship can be established, MAX gene mutations may need to be considered in suspected genetic forms of this disease.

Learning Points

- *MAX* encodes the MYC-associated protein X, which forms heterodimers with the MYC oncoprotein that increase transcription and heterodimers with MXD/MNT proteins that repress transcription.
- Germline inactivating *MAX* mutations are associated with hereditary pheochromocytoma and paraganglioma and a few other tumors.
- Several reports, including our case, report the development of PHPT in patients with *MAX* mutations. A causal relationship is currently speculative but deserves further investigation.

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Contributors

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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